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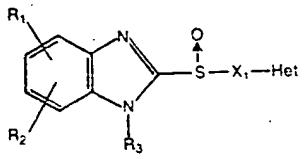
(54) Benzimidazoles and their pharmaceutical use.

(57) Substituted alkylsulfinylbenzimidazoles for use as pharmaceuticals or as active ingredients in pharmaceutical compositions, especially of the formula



wherein

R_1, R_2, R_3 and $-X_1$-Het are defined as given in the description. The compounds are used in the treatment or prevention of special gastrointestinal inflammatory diseases.

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BENZIMIDAZOLES AND THEIR PHARMACEUTICAL USE

The present invention relates to novel methods of treatment and to compositions employed in such methods. The present invention particularly relates to novel methods for preventing or treating gastrointestinal inflammatory diseases.

Certain pharmacological agents are known to have a cytoprotective effect on the gastrointestinal tract. This effect is manifest in the ability of such compounds to treat or prevent non-traumatically-induced, non-neoplastic inflammatory diseases of the gastrointestinal tract. The cytoprotective effects of prostaglandins are described in US Patent Specifications Nos. 4,083,998; 4,081,553 and 4,097,603.

Gastrointestinal inflammatory diseases include gastric inflammatory diseases such as gastric ulcer, duodenal ulcer and gastritis. Other gastrointestinal inflammatory diseases include Crohn's disease, inflammatory bowel disease, tropical and non-tropical sprue, infectious enteritis, colitis, ulcerative colitis, pseudomembranous colitis, diverticulitis, and allergenic and radiological inflammatory diseases.

As is known in the art, gastrointestinal inflammatory diseases are characterised by inflammation, specifically by the presence of oedema, characteristic inflammatory cells, i.e. leucocytes, histiocytes and macrophages, and, in some cases, necrosis and ulceration of the surface epithelium. These inflammatory diseases are known to be caused by a wide variety of agents which are present in and attack the surfaces of, the gastrointestinal tract, producing the

inflammatory disease response. Such agents include microorganisms (viruses and fungii), bacterial toxins, certain pharmaceutical agents (antibiotics and anti-inflammatory steroids), and chemical agents (bile salts, toxic household chemicals). Indeed, gastric acid itself is capable of attacking the stomach lining and producing the inflammatory state.

The prostaglandins and related fatty acid metabolites are a class of compounds from which most if not all the known cytoprotective agents are derived. Indeed, the endogenous production of prostaglandins by cells of the gastrointestinal tract apparently represents at least a part of a natural cytoprotective mechanism. For example, when a non-steroidal anti-inflammatory compound (NOSAC) is administered to a mammal, one effect is the inhibition of prostaglandin biosynthesis in the gastrointestinal tract, resulting in gastritis and gastrointestinal blood loss. However, when a prostaglandin is administered together with the non-steroidal anti-inflammatory compound, the untoward gastrointestinal consequences of NOSAC administration are alleviated. See United States Patent 3,927,213 (Lippman, "Prostaglandin E_2 and Derivatives for Reducing the Side Effects of Anti-inflammatory Agents",), issued 16 December 1975, and United States Patent 3,781,429 (Partridge, "Method of Inhibiting Ulcerogenisis induced by Non-Steroidal Anti-Inflammatory Agents"), issued 25 December 1973. Clinical reports of the reduction of gastrointestinal side effects from the concomitant administration of prostaglandins with NOSAC's are described by C. Johansson, et al., "Mucosal Protection by Prostaglandin E_2"), The Lancet, 10 Febraury 1979, p. 317, and M. M. Cohen, "Mucosal Protection by Prostaglandin E_2", The Lancet, 9 December 1978, p. 1253-1254.

Another method of preventing or treating certain gastrointestinal diseases, specifically gastric diseases, is by inhibition of gastric acid secretion. In situations where the integrity of the gastric mucosal barrier is compromised, gastric acid secretion can result in erosion of the epithelial cells with consequent inflammation and ulceration. Inhibition of such untoward gastric acid-induced effects can be achieved by either neutralization of the effects of the acid (e.g., antacid administration), or by administration of a pharmacological agent effective to inhibit gastric acid secretion.

One class of such agents effective to inhibit gastric acid secre-

tion are the gastric antisecretory prostaglandins. These substances are known to be effective in the treatment and cure of gastric and duodenal ulcers as a result of the inhibition of gastric secretion. See United States Patent 3,903,297 (Robert, "Method of Treatment and Prophylaxis of Gastric Hypersection and Gastric Duodenal Ulcers Using Prostaglandin Analogs"), issued 2 September 1975 and Robert, "Antisecretory Property of Prostaglandins", Prostaglandin Symposium of the Worcester Foundation for Experimental Biology, 16-17 October 1967, Inter-Science, N.Y., 1978, p. 47. Another important class of antisecretory agents are the histamine H_2 receptor antagonists, including metiamide and most especially cimetidine, N-cyano-N'-methyl-N''[2-[[(5-methyl-1H-imidazol-4-yl)methyl]thio]ethyl]gunanidine. See the Merck Index, 9th Edition, (APP-1 A-3) and Physicians' Desk Reference, 34th Edition, (1980), pages 1636-1641.

Accordingly, three classes of cytoprotective actions are known to affect beneficially gastrointestinal inflammatory diseases: (1) direct cytoprotective effects, such as those exhibited by the prostaglandins, (2) inhibitory effects on the untoward consequences of prostaglandin synthetase inhibition, e.g., such as are produced by NOSAC administration, and (3) inhibitory effects on the untoward effects of gastric acid secretion, such as are produced by antacids and gastric antisecretory agents such as prostaglandins and histamine H_2 receptor antagonists. Although the first of these three effects (protection from non-gastric acid and non-NOSAC induced inflammatory diseases) is the only one which can unconditionally be referred to as a "cytoprotective" effect, nonetheless both direct cytoprotective effects and the protective effects of the inhibition of untoward NOSAC-induced effects are commonly known in the art as "cytoprotective". Accordingly, the term "cytoprotective effect", "cytoprotective action", and "cytoprotection" as used herein will refer both to direct cytoprotection (U.S. Patents 4,083,998, 4,081,553, and 4,097,603) and inhibition of NOSAC-induced effects (U.S. Patents 3,927,213 and 3,781,429), but not protection against gastric-acid induced inflammatory diseases.

Although the prostaglandins represent a class of agents which, in some cases, are both "cytoprotective" and inhibitors of gastric secretion, not all gastric antisecretory agents exhibit appreciable cytoprotective effects. Moreover, antacids which effectively neutralize gastric acid are not cytoprotective. Cimetidine, for example, is an

example of a highly potent inhibitor of gastric secretion, which is devoid of appreciable cytoprotective effects. See A. Robert, "Cytoprotection Against Acidified Aspirin: Comparison of Prostaglandin, Cimetidine, and Probanthine", Gastroenterology 76:1227 (May 1979), and references cited therein indicating any apparent cytoprotective effects of cimetidine are related to its antisecretory property. See also Kauffman, G. L., et al., "Cimeditine Does Not Inhibit Indomethacin-Induced Small Bowel Ulceration in the Rat", Proc. of the Soc. Exp. Biol. Med. 161:512-4 (1979).

The present invention specifically relates to heterocyclylalkylsulfinylbenzimidazoles, heretofore known to be useful as gastric antisecretory agents and, therefore, useful in the treatment of gastric ulcers. See United States Patent 4,045,563 and European Published Patent Application 0 005 129 (abstracted and published as Derwent Farmdoc CPI No. 79478B). For at least certain of these substituted benzimidazoles, the inhibition of gastric secretion is accomplished by direct action on the acid-secreting parietal cells of the stomach, specifically through inhibition of potassium ion-dependent ATPase. See, for example, Lars Olbe, et al., "Properties of a New Class of Gastric Acid Inhibitors", Scand. J. Gastroenterol, 14:131-135 (1979, Supp 55).

PRIOR ART

Heterocyclylalkylsulfinylbenzimidazoles are known in the art, as are methods of using these compounds to reduce gastric acid secretion. See the above references. Also known in the art are other gastric antisecretory agents, e.g., the prostaglandins and histamine H_2 receptor antagonists, such as cimetidine and metiamine. See also references cited above.

Finally, also known in the art are cytoprotective uses for certain prostaglandins, including gastric antisecretory prostaglandins. However, the absence of comparable cytoprotective effects for other gastric antisecretory agents unrelated to gastric antisecretory property is also known. See A. Robert, Gastroenterology 76:1227 (May 1979), cited above.

SUMMARY OF THE INVENTION

The present invention particularly provides

(a) a method for the treatment or prevention of a non-gastric-acid-induced, non-traumatically-induced, non-neoplastic gastro-

intestinal inflammatory disease in a mammal suffering from or particularly susceptible to the development of said disease, which comprises:

administering orally to said mammal an amount of a cytoprotective heterocyclylalkylsulfinylbenzimidazole effective to treat or prevent said disease;

(b) an oral pharmaceutical composition in unit dosage form for the treatment or prevention of a non-gastric-acid-induced, non-traumatically-induced, non-neoplastic gastrointestinal inflammatory disease in a mammal suffering from or susceptible to the development of said disease which comprises:

(1) an amount of a cytoprotective heterocyclylalkylsulfinylbenzimidazole

(a) effective to treat or prevent said disease, and

(b) less than the gastric antisecretory ED_{50} of said cytoprotective heterocyclylalkylsulfinylbenzimidazole; and

(2) a pharmaceutically-acceptable carrier; and

(c) a method of protecting the gastrointestinal tract in a mammal from the untoward non-gastric-acid-induced effects of exposure to gastrointestinally injurious agents, which comprises:

administering orally to said mammal a non-antisecretory (less than antisecretory ED_{50}) amount of a cytoprotective heterocyclylalkylsulfinylbenzimidazole effective to prevent or ameliorate said effects.

Cytoprotective heterocyclylalkylsulfinylbenzimidazoles, together with the manner of making them and their pharmaceutical compositions for gastric antisecretory use are described in United States Patent 4,045,563 and European Published Patent Application 0 005 152, published 31 October 1979 (also abstracted and published at Derwent Farmdoc CPI No. 79478B).

Accordingly, said cytoprotective heterocyclylalkylsulfinylbenzimidazoles include a compound of formula I

wherein R_1 and R_2, being the same or different, are

(a) hydrogen,

(b) alkyl of one to 4 carbon atoms, inclusive,

(c) fluoro, iodo, chloro, or bromo,

(d) cyano,

(e) carboxy,

(f) carboxyalkyl of 2 to 5 carbon atoms, inclusive,

(g) alkoxycarbonyl of 2 to 5 carbon atoms, inclusive,

(h) alkoxycarbonylalkyl of 3 to 9 carbon atoms, inclusive, with the proviso that each alkyl group therein is of one to 4 carbon atoms, inclusive,

(i) carbamoyl,

(j) carbamoyloxy,

(k) hydroxy,

(l) alkoxy of one to 5 carbon atoms, inclusive,

(m) hydroxyalkyl of one to 7 carbon atoms, inclusive,

(n) trifluoromethyl, or

(o) alkylcarbonyl of one to 4 carbon atoms, inclusive,

wherein R_3 is

(a) hydrogen,

(b) alkyl of one to 4 carbon atoms, inclusive,

(c) alkylcarbonyl of one to 4 carbon atoms, inclusive,

(d) alkoxycarbonyl of 2 to 5 carbon atoms, inclusive,

(e) carbamoyl,

(f) alkylcarbamoyl of 2 to 5 carbon atoms,

(g) dialkylcarbamoyl of 3 to 9 carbon atoms, inclusive, with the proviso that each alkyl is of one to 4 carbon atoms, inclusive,

(h) alkylcarbonylmethyl of 3 to 5 carbon atoms, inclusive,

(i) alkoxycarbonylmethyl of 3 to 5 carbon atoms, inclusive, or

(j) alkylsulfonyl of one to 4 carbon atoms, inclusive;

wherein X_1 is alkylene of one to 4 carbon atoms, inclusive, with one to 4 carbon atoms, inclusive, in a chain, being straight or branched; and

wherein Het is

(a) imidazolyl,

(b) imidazolinyl,

(c) benzimidazolyl,

(d) thiazolyl,

(e) thiazolinyl,

(f) quinolyl,

(g) piperidyl,

(h) pyridyl, or

(i) imidazolyl, imidazolinyl, benzimidazolyl, thiazolyl, thia-

zolinyl, quinolyl, piperidyl, pyridyl, or pyridyl substituted by one, two, or 3 alkyl of one to 4 carbon atoms, inclusive, fluoro, iodo, chloro, or bromo, or

wherein R_1 and R_2 are hydrogen, alkyl, halogen, methoxycarbonyl, ethoxycarbonyl, alkoxy, or alkylcarbonyl, being the same or different, R_3 is hydrogen, and $-X_1$-Het taken together is a moiety of formula II

wherein R_4, R_5, and R_6, being the same or different, are (a) hydrogen, (b) methyl, (c) methoxy, (d) ethoxy, (e) methoxyethoxy, or (f) ethoxyethoxy, with the provisos that (1) R_3, R_4, and R_5 are not all hydrogen, and (2) two of R_3, R_4, and R_5 are hydrogen only when the third is not methyl, and

wherein R_7 is hydrogen, methyl, or ethyl;

and the pharmacologically acceptable salts thereof.

Most especially included in the scope of said cytoprotective heterocyclylalkylsulfinylbenzimidazoles are compounds selected from the group consisting of

2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(4,6-dimethyl)benzimidazole,

2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,

2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(4,6-dimethyl)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-ethoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3-methyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl)-benzimidazole,

2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methyl)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-benzimidazole, or

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-chloro)-benzimidazole.

Also included within the scope of said cytoprotective heterocyclylalkylsulfinylbenzimidazoles are compounds selected from the group

2-[2-pyridylmethylsulfinyl]benzimidazole [i.e., timoprazole],

2-[2-pyridylmethylsulfinyl]-(4,6-dimethyl)benzimidazole,

2-[2-pyridylmethylsulfinyl]-(5-ethyl)benzimidazole,

2-[2-pyridylmethylsulfinyl]-(4-methyl,6-chloro)benzimidazole,

2-[2-pyridylmethylsulfinyl]-(5-methoxy)benzimidazole,

2-[2-pyridylmethylsulfinyl]-(5-hydroxy)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-acetyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-carboxy)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-carbethoxy)benzimidazole,
2-[2-(4-chloro)pyridylmethylsulfinyl]benzimidazole,
2-[2-(5-methyl)pyridylmethylsulfinyl]benzimidazole,
2-[2-pyridylmethylsulfinyl]-N-methylbenzimidazole,
2-[2-pyridyl-(methyl)methylsulfinyl]benzimidazole,
2-[2-pyridylmethylsulfinyl]-(4-methyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(N-acetyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(N-methoxycarbonyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-methyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-chloro)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-isopropyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-t-butyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-n-propyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(N-carbamoyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(N-methylcarbamoyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(N-acetylmethyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(N-ethoxycarbonylmethyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(N-methylsulfonyl)benzimidazole,
2-[2-(4-methyl)pyridylmethylsulfinyl]-(5-methyl)benzimidazole,
2-[2-(5-methyl)pyridylmethylsulfinyl]-(5-methyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(6-chloro)benzimidazole,
2-[2-pyridyl-(ethyl)methylsulfinyl]benzimidazole,
2-[2-pyridyl-(ethyl)methylsulfinyl]-(5-chloro)benzimidazole,
2-[2-pyridyl-(methyl)methylsulfinyl]-(5-ethyl)benzimidazole,
2-[2-(3-methyl)pyridylmethylsulfinyl]benzimidazole,
2-[2-(5-ethyl)pyridylmethylsulfinyl]-(5-methyl)benzimidazole,
2-[2-(5-ethyl)pyridylmethylsulfinyl]benzimidazole,
2-[2-pyridyl-(ethyl)methylsulfinyl]-(5-ethyl)benzimidazole,
2-[2-pyridyl-(methyl)methylsulfinyl]-(5-cyano)benzimidazole,
2-[2-pyridyl-(methyl)methylsulfinyl]-(5-trifluoro)benzimidazole,
2-[2-pyridyl-(ethyl)methylsulfinyl]-(5-methyl)benzimidazole,
2-[2-pyridyl-(ethyl)methylsulfinyl]-(5-cyano)benzimidazole,
2-[2-pyridyl-(ethyl)methylsulfinyl]-(5-trifluoro)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(4-chloro)benzimidazole,

2-[2-pyridyl-(isopropyl)methylsulfinyl]benzimidazole,

2-[2-pyridyl-(methyl)methylsulfinyl]-(5,6-dimethyl)benzimidazole, and

2-[2-pyridylmethylsulfinyl]-(5,6-dimethyl)benzimidazole.

The present invention in part relates to compositions and methods for treatment of non-gastric-acid-induced, non-traumatically-induced, non-neoplastic gastrointestinal inflammatory diseases. This term of art is used in its ordinary and conventional sense, such as United States Patent 4,083,998, cited above.

Mammals suffering from these inflammatory diseases are readily diagnosed by an attending physician or veterinarian of ordinary skill in the art. Mammals particularly susceptible to the development of these diseases are those mammals whose environment or medical history provides a known predisposition to gastrointestinal inflammatory disease. For example, mammals especially susceptible to gastric inflammatory diseases include those:

(1) with a history of multiple episodes of gastric or duodenal ulceration,

(2) with a history of chronic and excessive ethanol consumption,

(3) with a recent acute exposure to a cytodestructive dose of ionizing radiation,

(4) with an acute or chronic ingestive exposure to cytodestructive chemical agents, including cytodestructive chemical agents, or

(5) with a recent exposure to pathogens capable of producing cytodestructive conditions. Similarly, those mammals with a history of colitis, especially ulcerative colitis, are likewise known in the art to be particularly susceptible to recurrence of this gastrointestinal inflammatory disease.

Mammals to whom the cytoprotective heterocyclylalkylsulfinylbenzimidazoles are administered are particularly and especially humans, although other valuable domestic animals and experimental animals are also included within the scope of the present invention.

In accordance with the novel methods employing these cytoprotective heterocyclylalkylsulfinylbenzimidazoles, the present invention provides for oral administration. Accordingly, oral administration described in European Published Patent Application 0 005 152 and United States Patent 4,045,563 is conveniently employed.

Appropriate oral pharmaceutical compositions are formulated for

use in accordance with the present invention. Such pharmaceutical compositions are employed as described in European Published Patent Application 0 005 152 and United States Patent 4,045,563, except that in place of an antisecretory amount of the heterocyclylalkylsulfinylbenzimidazole, a cytoprotective amount, i.e., an amount effective to treat or prevent the non-traumatically-induced, non-neoplastic gastrointestinal inflammatory disease, is employed in the composition.

Particularly and especially, the compositions employed in accordance with the present invention are in a unit dosage form, as that term is employed in the art, and contain in the unit dosage an amount of the cytoprotective heterocyclylalkylsulfinylbenzimidazole which is both effective to treat or prevent the gastric inflammatory disease and less than the gastric antisecretory ED_{50} (dose effective to inhibit 50% of basal acid secretion) of the cytoprotective heterocyclylalkylsulfinylbenzamidizole. Hence these compositions, which by definition provide insubstantial gastric antisecretory effects, are nonetheless surprisingly and unexpectedly effective as cytoprotective pharmaceutical compositions.

The amount of the cytoprotective heterocyclylalkylsulfinylbenzimidazole effective to treat or prevent the gastrointestinal inflammatory diseases is an amount which varies according to the mammal being treated, the severity of the disease, the route of administration selected, and the particular heterocyclylalkylsulfinylbenzimidazole being employed. Ordinarily, the relative potencies of these cytoprotective heterocyclylalkylsulfinylbenzimidazoles are determined by tests in standard laboratory animals described in Example 1 and employed in accordance with the present method in proportion to their relative potencies. Accordingly, such determinations are readily within the skill of pharmacologists in the art.

These cytoprotective heterocyclylalkylsulfinylbenzimidazoles are accordingly administered one to 6 times daily at dosages between from about 0.1 µg to about 100 mg/kg/day orally.

Prevention of the gastrointestinal inflammatory diseases results in the reduction of the incidence and severity of ulceration ordinarily produced by the disease, including total prevention of the inflammatory process. Treatment results in accelerated and more complete and satisfactory healing of ulcers and other manifestations of the inflammatory process. Accordingly the present invention pro-

vides for the pharmacological use of heterocyclylalkylsulfinylbenzimidazoles at lower effective doses than heretofore possible and provides a surprisingly and unexpectedly valuable means of treating and preventing gastrointestinal disease that was not heretofore available with these compounds.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Example 1 Effective Dose for Gastric Acid Secretion Inhibition by timoprazole, 2-[2-pyridylmethylsulfinyl]benzimidazole

Groups of rats were fasted with restraint for 36 hours. To the rats in each group, 2 ml of vehicle (10% Emulphor, 10% ethanol, 80% water) or timoprazole (at a selected dosage in vehicle) were administered orally one hour prior to pylorous ligation performed under ether anesthesia. Four hours later, rats were sacrificed by CO_2 asphyxiation and their gastric contents were collected for measurement of titratable acid output. Acid outputs from timoprazole-treated rats, as percentage of output from control (vehicle alone) rats, were:

Acid Output (percent of control) Oral Administration	Dose mg/kg
80*	0.01
80*	0.1
80*	1.0
60	3.0
55	10.0
--	30.0
30	100.0

* Not significantly ($P<0.05$) less than controls.

Thus, by oral administration, the ED_{50} for inhibition by timoprazole of gastric acid secretion is approximately 12 mg/ml.

Example 2 Effect of timoprazole on ethanol-induced gastric lesions

A. Four groups of rats, standard laboratory animals for determining cytoprotective effects of pharmacological agents, are fasted for 24 hr and then treated orally with (a) timoprazole (in vehicle), (b) cimetidine (in vehicle), or (c) vehicle (10% Emulphor, 10% EtOH, 80% water). Thirty min later, the rats are challenged with an oral 1 ml dose of 80% aqueous ethanol, a standard agent for inducing gastric cytodestruction. One hr later, the rats are sacrificed (carbon dioxide asphyxiation) and the gastric tissues examined. Rats treated with timoprazole at 0.3, 1, 3, or 10 mg/kg demonstrate no gastric ulceration. Rats treated with a dose of 0.3 mg/kg show traces of mild ulceration. In contrast, rats treated with vehicle only or with cimetidine at 0.3, 1.0, 3.0 or 10.0 mg/kg all demonstrate gastric ulcers, although a slight decrease in the number of ulcers is noted in the cimetidine-treated animals. The ED_{50} of timoprazole for gastric acid secretion inhibition is at least ten times greater than the lowest cytoprotective dose observed in this experiment.

B. A further experiment is undertaken to rule out gastric emptying as a factor in the cytoprotection observed in part A above. In this experiment timoprazole was given orally at 0.01, 0.1, or 1.0 mg/kg to groups of rats and a further group of rats is treated with vehicle (same as in part A) only. As above, the rats are fasted for 24 hr prior to treatment. Groups of rats are then sacrificed 5, 15, and 30 min after timoprazole ingestion. No significant changes in gastric volume between rats treated with vehicle and rats treated with timoprazole is observed at any of the three sacrifice times. Accordingly, fluid accumulation in the stomach is not a factor in the cytoprotection observed in part A.

C. A further experiment is performed to determine the lowest dose of timoprazole at which 50% of the animals treated exhibit no gastric ulceration (ED_{50}), employing a vehicle with less "mild irritant" effects than in part A. Groups of rats are fasted for 24 hr and then treated orally or subcutaneously with timoprazole at 1, 3, or 10 mg/kg in vehicle (5% EtOH, 1% Emulphor in water) at 30 min before

ethanol challenge. The rats are sacrificed one hour after timoprazole administration and the extent of gastric ulceration determined. Subcutaneous administration of timoprazole did not significantly reduce the number of ulcers compared to control (vehicle-treated) rats. Oral administration produced a significant reduction in ulceration at all dosages tested and the ED_{50} is determined to be below 1 mg/kg.

D. Because mild gastric irritants, e.g., 20% ethanol, are known to stimulate endogenous prostaglandin production, with consequent cytoprotection effects being observed, a further experiment is undertaken to determine whether timoprazole acts as a mild irritant (i.e., by stimulating endogenous cytoprotective prostaglandin production), or exerts a directly cytoprotective effect. In this experiment, rats are treated with timoprazole (5 mg/kg orally), but in each group of rats half the animals are pretreated with a NOSAC, indomethacin, 1 hr prior to treatment with timoprazole. One hour after ethanol challenge, the rats are sacrificed. However, no significant difference is observed between rats receiving indomethicin and those not receiving indomethicin. Accordingly, the cytoprotective effects of timoprazole are not mediated by endogenous prostaglandin production.

Example 3 Cytoprotective effect of timoprazole against thermally induced gastric ulceration.

Following the procedure of Example 2A, but employing boiling water (greater than 85-95°C) in place of 80% ethanol, there is obtained a uniform reduction in the incidence and severity of ulcers in timoprazole-treated rats (0.3, 1.0, 3.0, and 10.0 mg/kg) as compared to rats receiving vehicle only. Using the ulcer incidence (ulcers/stomach) scoring system of Robert (U.S. Patent 4,097,603, column 4, lines 41-53), the control group exhibits a score of 8.0, while the treated groups exhibit scores of 7.6 (0.3 mg/kg), 5.0 (1.0 mg/kg), 3.9 (3.0 mg/kg), and 4.0 (10.0 mg/kg).

Example 4 Cytoprotective effect of timoprazole against acid-induced gastric ulceration

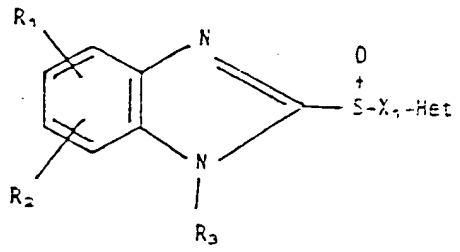
Following the procedure of Example 2A but employing 0.6N HCl in place of 80% ethanol, there is obtained a uniform reduction in the incidence and severity of ulcers in timoprazole-

treated rats (1, 3, 10 and 30 mg/kg) as compared to rats receiving vehicle only. Using the ulter incidence (ulcers/stomach) scoring system of Robert (US Patent 4 097 603, column 4, lines 41-53), the control group exhibits a score of 9.6, while the treated groups exhibit scores of 6.7(1 mg/kg), 2.2 (3 mg/kg), 1.5 (10 mg/kg) and 1.2 (30 mg/kg).

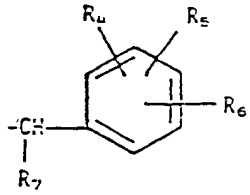
Example 5

2-[2-pyridylmethylsulfinyl]benzimidazole HCl (100 g) is mixed with lactose (527.4 g), potato starch (509.1 g), and colloidal silicic acid (96 g). The mixture is moistened with 10% solution of gelatin and is ground through a 12-mesh sieve. After drying, potato starch (480 g), talc (150 g) and magnesium stearate (15 g) are added and the mixture thus obtained is pressed into 10,000 tablets, with each containing 10 mg of active substance. Tablets containing 2.5 mg of active substance are similarly prepared by using 25 g of 2-[2-pyridylmethylsulfinyl]benzimidazole.HCl in the formulation.

FORMULAS



(I)



(II)

ethod for the prevention of a non-gastric acid-
non-traumatically-induced, non-neoplastic
ntestinal inflammatory disease in a mammal suscept-
the development of the disease, which comprises
tering orally to the mammal an amount of a cyto-
ve alkylsulfinylbenzimidazole.

ethod for protecting the gastrointestinal tract in
from non-gastric acid-induced effects of potential
to gastrointestinally injurious agents, which
s administering orally to the mammal an amount of
tective alkylsulfinylbenzimidazole.

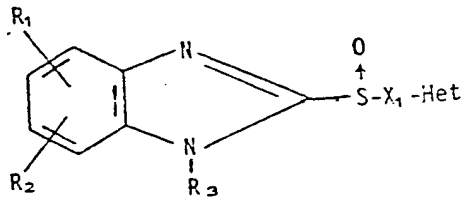
ethod according to claim 1 or claim 2, in which the
dministered is less than the gastric antisecretory
the alkylsulfinylbenzimidazole.

alkylsulfinylbenzimidazole, for use in the
nt or prevention of non-gastric acid-induced, non-
ically-induced, non-neoplastic gastrointestinal
tory disease.

alkylsulfinylbenzimidazole, for use in protecting
rointestinal tract of a mammal from non-gastric
duced effects of potential or actual exposure to
ntestinally injurious agents.

oral pharmaceutical composition, in unit dosage
ich comprises a cytoprotective alkylsulfinylben-
le in an amount less than the gastric antisecretory
the cytoprotective heterocyclylalkylsulfinylbenz-
le, and a pharmaceutically acceptable carrier.

method, compound or composition according to any
g claim, in which the alkylsulfinylbenzimidazole
pound of formula I



I

wherein R_1 and R_2, being the same or different, are

(a) hydrogen,

(b) alkyl of one to 4 carbon atoms, inclusive,

(c) fluoro, iodo, chloro, or bromo,

(d) cyano,

(e) carboxy,

(f) carboxyalkyl of 2 to 5 carbon atoms, inclusive,

(g) alkyloxycarbonyl of 2 to 5 carbon atoms, inclusive,

(h) alkoxycarbonylalkyl of 3 to 9 carbon atoms, inclusive, with the proviso that each alkyl group therein is of one to 4 carbon atoms, inclusive,

(i) carbamoyl,

(j) carbamoyloxy,

(k) hydroxy,

(l) alkoxy of one to 5 carbon atoms, inclusive,

(m) hydroxyalkyl of one to 7 carbon atoms, inclusive,

(n) trifluoromethyl, or

(o) alkylcarbonyl of one to 4 carbon atoms, inclusive,

wherein R_3 is

(a) hydrogen,

(b) alkyl of one to 4 carbon atoms, inclusive,

(c) alkylcarbonyl of one to 4 carbon atoms, inclusive,

(d) alkoxycarbonyl of 2 to 5 carbon atoms, inclusive,

(e) carbamoyl,

(f) alkylcarbamoyl of 2 to 5 carbon atoms,

(g) dialkylcarbamoyl of 3 to 9 carbon atoms, inclusive, with the proviso that each alkyl is of one to 4 carbon atoms, inclusive,

(h) alkylcarbonylmethyl of 3 to 5 carbon atoms, inclusive,

(i) alkoxycarbonylmethyl of 3 to 5 carbon atoms, inclusive, or

(j) alkylsulfonyl of one to 4 carbon atoms, inclusive;

wherein X_1 is alkylene of one to 4 carbon atoms, inclusive, with one to 4 carbon atoms, inclusive, in a chain, being straight or branched; and

wherein Het is

(a) imidazolyl,

(b) imidazolinyl,

(c) benzimidazolyl,

(d) thiazolyl,

(e) thiazolinyl,

(f) quinolyl,

(g) piperidyl,

(h) pyridyl, or

(i) imidazolyl, imidazolinyl, benzimidazolyl, thiazolyl, thiazolinyl, quinolyl, piperidyl, pyridyl, or pyridyl substituted by one, two, or 3 alkyl of one to 4 carbon atoms, inclusive, fluoro, iodo,

benzimidazole,

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(4,6-dimethyl)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-ethoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3-methyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl)-benzimidazole,

2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methyl)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-benzimidazole, or

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-chloro)-benzimidazole.

9. A method, compound or composition according to any of claims 1 to 7 in which the alkylsulfinylbenzimida-

zole is selected from

2-[2-pyridylmethylsulfinyl]benzimidazole,
2-[2-pyridylmethylsulfinyl]-(4,6-dimethyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-ethyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(4-methyl,6-chloro)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-methoxy)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-hydroxy)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-acetyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-carboxy)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-carbethoxy)benzimidazole,
2-[2-(4-chloro)pyridylmethylsulfinyl]benzimidazole,
2-[2-(5-methyl)pyridylmethylsulfinyl]benzimidazole,
2-[2-pyridylmethylsulfinyl]-N-methylbenzimidazole,
2-[2-pyridyl-(methyl)methylsulfinyl]benzimidazole,
2-[2-pyridylmethylsulfinyl]-(4-methyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(N-acetyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(N-methoxycarbonyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-methyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-chloro)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-isopropyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-t-butyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(5-n-propyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(N-carbamoyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(N-methylcarbamoyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(N-acetylmethyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(N-ethoxycarbonylmethyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(N-methylsulfonyl)benzimidazole,
2-[2-(4-methyl)pyridylmethylsulfinyl]-(5-methyl)benzimidazole,
2-[2-(5-methyl)pyridylmethylsulfinyl]-(5-methyl)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(6-chloro)benzimidazole,
2-[2-pyridyl-(ethyl)methylsulfinyl]benzimidazole,
2-[2-pyridyl-(ethyl)methylsulfinyl]-(5-chloro)benzimidazole,
2-[2-pyridyl-(methyl)methylsulfinyl]-(5-ethyl)benzimidazole,
2-[2-(3-methyl)pyridylmethylsulfinyl]benzimidazole,
2-[2-(5-ethyl)pyridylmethylsulfinyl]-(5-methyl)benzimidazole,
2-[2-(5-ethyl)pyridylmethylsulfinyl]benzimidazole,
2-[2-pyridyl-(ethyl)methylsulfinyl]-(5-ethyl)benzimidazole,

2-[2-pyridyl-(methyl)methylsulfinyl]-(5-cyano)benzimidazole,
2-[2-pyridyl-(methyl)methylsulfinyl]-(5-trifluoro)benzimidazole,
2-[2-pyridyl-(ethyl)methylsulfinyl]-(5-methyl)benzimidazole,
2-[2-pyridyl-(ethyl)methylsulfinyl]-(5-cyano)benzimidazole,
2-[2-pyridyl-(ethyl)methylsulfinyl]-(5-trifluoro)benzimidazole,
2-[2-pyridylmethylsulfinyl]-(4-chloro)benzimidazole,
2-[2-pyridyl-(isopropyl)methylsulfinyl]benzimidazole,
2-[2-pyridyl-(methyl)methylsulfinyl]-(5,6-dimethyl)benzimidazole,
and
2-[2-pyridylmethylsulfinyl]-(5,6-dimethyl)benzimidazole.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

0045200

EP 81303416.2

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
X	EP - A1 - 0 005 129 (AKTIEBOLAGET HÄSSLE) * Claims 1-9 * --	4-9
X	US - A - 4 045 563 (BERNTSSON, CARLSSON, GARBERG, JUNGGREN, SJÖSTRAND, VON WILTKEN SUNDELL) * Columns 1,2,9-24 * --	4-9
X	GB - A - 1 525 958 (BERNTSSON et al.) * Pages 1,2,5,11-13,15,16 * --	4-9
	US - A - 4 045 564 (BERNTSSON et al.) * Columns 1-5, 7-12 * --	4-9
X	DE - A1 - 2 548 340 (AB HÄSSLE) * Claims 1-58 * --	4-9

CLASSIFICATION OF THE APPLICATION (Int. Cl.)

A 61 K 31/415
A 61 K 31/425
A 61 K 31/47
A 61 K 31/445
A 61 K 31/44
C 07 D 235/28
C 07 D 401/12
C 07 D 403/12
C 07 D 417/12

TECHNICAL FIELDS SEARCHED (Int. Cl.)

A 61 K 31/00
C 07 D 235/00
C 07 D 401/00

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 4-6
Claims searched incompletely: 7-9
Claims not searched: 1-3
Reason for the limitation of the search:

Method for treatment of the human or animal body by therapy, Article 52(4) EPC

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

Place of search	Date of completion of the search	Examiner
VIENNA	20-10-1981	MAZZUCCO

EPO Form 1505.1 06.78

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

0045200
Application number

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	GB - A - 1 152 814 (LAB. CASSENNE) * Pages 1,5,6,8 * --	4-6	
	DE - A1 - 2 840 591 (HOFFMANN - LA ROCHE) * Pages 4-9 * & US-A-4 248 880 (03-02-1981) --	4-9	
	FR - A1 - 2 319 346 (THE WELLCOME FOUNDATION LTD) * Pages 3,4 * & AU-A-16 437/76 ----	4-6	TECHNICAL FIELDS SEARCHED (Int. Cl.)

EPO Form 1505.3 06.78